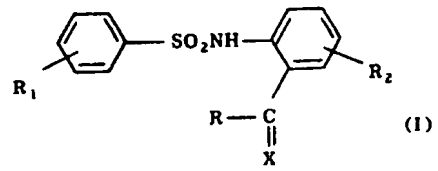
86-279735/43 B05 VEFL 21.12.84
VEB FAHLBERG LIST CHEM *DE 3544-409-A
21.12.84-DD-271462 (16.10.86) A61k-31/18 C07c-143/78
2-Aryl:sulphonamido:phenyl ketone and oxime derivs. - used as cyclo-oxygenase and lipoxygenase inhibitors, e.g. for treating asthma, inflammation and thrombosis
C86-120834

B(10-A8, 10-A18, 12-A7, 12-D2, 12-D3, 12-D7, 12-D9, 12-E1, 12-F1B, 12-F5, 12-G1B1, 12-H3, 12-K2)

Pharmaceutical compsn. contains, as active agent, a 2-arylsulphonamido benzophenone or acetophenone, or its oxime deriv., of formula (I):



(I)

R = methyl, phenyl or p-substd. phenyl;
R_1 = 1-18C alkyl, 1-18C alkoxy, amino or acylamino;
R_2 = H, halogen, NO_2 or NHR_3;
R_3 = H, acyl or arylsulphonyl;
X = O or NOR_4;
R_4 = H, 1-12C alkyl, aralkyl, COR_5 or $CONHR_5$;
R_5 = aliphatic or aromatic gp.

Prepn. of (I) comprises reacting a 2-amino-phenone, a substd. benzenesulphonyl halide and a liq. organic base (or a soln. of an organic base in an inert solvent) in a closed flask at room temp.

The obtd. (I; X = O) is opt. converted into an oxime by reaction with hydroxylamine hydrochloride in presence of a base (pref. KOAc or pyridine) in an organic solvent (pref. EtOH or a lower alkyl glycol) at 50-150°C.

The following cpds. (I) are new (BSA = benzene-sulphonamido; PTSA = p-toluenesulphonamido):
2-PTSA - benzophenone oxime (Ia);
2-PTSA - acetophenone oxime;
2-(p-ethyl-BSA) - acetophenone and its oxime;
2-(p-pentoxy-BSA) - benzophenone and its oxime;
2-(p-dodecyloxy-BSA) - benzophenone and its oxime;
2-(p-methoxy-BSA) - acetophenone and its oxime;
2-(p-acetamino-BSA) - benzophenone and its oxime;
2- PTSA-5-chloro - benzophenone and its oxime;
2-(p-methoxy-BSA)-5-nitro - benzophenone oxime; and
2-(p-decyloxy-BSA) - benzophenone oxime.

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USE/ADVANTAGE

(I) are universal inhibitors of both lipoxygenase and cyclooxygenase, and hence inhibit the arachidonic acid cascade. They have very low toxicity (no acute toxicity in rats at 6 g/kg p.o.), are free from side-effects and have gastroprotective rather than ulcerogenic activity.

(I) are useful for treating
(i) bronchial asthma, asthmoid bronchitis, obstructive pulmonary emphysema and other bronchoconstrictory states;
(ii) allergic diseases, e.g. atopic dermatitis, allergic rhinitis, urticaria, angiooedema, contact dermatitis, allergic conjunctivitis and allergic gastrointestinal disorders;
(iii) inflammation, esp. purulent inflammation and rheumatic/arthritic diseases;
(iv) thrombosis (esp. thrombophlebitis), including prophylaxis of thrombosis associated with chronic ischaemic heart disease, post-treatment of myocardial infarct, chronic recurrent thrombosis and chronic thrombophlebitis;
(v) arterial hypertension, esp. in pulmonary circulation; and
(vi) smooth muscle spasms, esp. in the respiratory and urogenital tracts and vascular musculature.

(I) are also antiartherosclerotic, cardiac circulatory protective, gastroprotective and antimetastatic agents. They may be administered parenterally or pref. orally, at daily doses of 0.05-100 (pref. 0.1-50) mg/kg.

EXAMPLE

A mixt. of 14 g 2-PTSA-benzophenone, 6 g $NH_2OH.HCl$, 16 g KOAc and 100 ml EtOH was refluxed 3 hrs., filtered and treated with water to ppte. (Ia), m. pt. 156-180°C (aq. EtOH), as a syn/anti-mixt.

This cpd. reduced arachidonic acid-induced contractions in isolated rabbit pulmonary arteries by 80-85% at 50 µM, inhibited carrageenin-induced rat paw oedema by 56% after 1 hr. at 50 mg/kg, had ID_{50} 75 µM against rabbit reticulocyte lipoxygenase and had ID_{50} 100 µM against isolated sheep seminal vesicular cyclooxygenase. (44pp941JWDwgNo0/0).

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